Anaesthesia 2018, 73, 480–489 doi:10.1111/anae.14166

Review Article

Intravenous dexamethasone for prophylaxis of postoperative nausea and vomiting after administration of long-acting neuraxial opioids: a systematic review and meta-analysis

S. Grape,[1] I. Usmanova,[2] K. R. Kirkham[3] and E. Albrecht[4]

1 Lecturer, 2 Resident, Department of Anaesthesia and Intensive Care Medicine, Valais Hospital, Sion, Switzerland
3 Lecturer, Department of Anaesthesia, Toronto Western Hospital, University of Toronto, Canada
4 Program Director of Regional Anaesthesia, Department of Anaesthesia, Lausanne University Hospital, Lausanne, Switzerland

Summary

Long-acting neuraxial opioids provide excellent analgesia after surgery, but are associated with higher rates of postoperative nausea and vomiting. Dexamethasone effectively prevents postoperative nausea and vomiting after general anaesthesia, but its value in patients receiving long-acting neuraxial opioids is undetermined. Therefore, the objective of this meta-analysis was to assess the prophylactic anti-emetic efficacy of intravenous (i.v.) dexamethasone in this population. The study methodology followed the PRISMA statement guidelines. The primary outcome was the need for rescue anti-emetics during the first 24 postoperative hours, analysed according to the dose of dexamethasone (low-dose 2.5–5.0 mg; intermediate dose 6.0–10.0 mg), timing of administration (beginning or end of surgery) and route of long-acting opioid administration (intrathecal or epidural). Additionally, the rates of complications (restlessness, infection, hyperglycaemia) were sought. Thirteen trials were identified, representing a total of 1111 patients. When compared with placebo, intravenous dexamethasone reduced the need for rescue anti-emetics (risk ratio (95% CI) 0.44 (0.35–0.56); $I^2 = 43\%$; $p < 0.00001$; quality of GRADE evidence: moderate), without differences between dexamethasone doses (p for sub-group difference = 0.67), timing of administration (p for sub-group difference = 0.32) or route of long-acting opioid (p for sub-group difference = 0.10). No patients developed infection or restlessness among trials that sought these complications. No trial measured blood glucose levels. In conclusion, there is enough evidence to state that intravenous dexamethasone provides effective anti-emetic prophylaxis during the first 24 postoperative hours in patients who receive long-acting neuraxial opioids.

Correspondence to: E. Albrecht
Email: eric.albrecht@chuv.ch
Accepted: 17 October 2017
Keywords: dexamethasone; epidural opioids; neuraxial opioids; postoperative nausea and vomiting; spinal opioids

Introduction

Long-acting neuraxial opioids prolong the duration of sensory block after spinal anaesthesia and provide excellent analgesia after surgery [1]. However, postoperative nausea and vomiting is a frequent side-effect, affecting more than 50% of patients, which has the potential to significantly worsen postoperative recovery [2]. Intravenous (i.v.) dexamethasone is an effective prophylactic

anti-emetic against postoperative nausea and vomiting after general anaesthesia [3], but its efficacy in patients who receive long-acting neuraxial opioids remains undetermined following conflicting results from several randomised controlled trials [4–7]. A previous meta-analysis, limited to female patients, partially addressed this question, but its conclusion was positive only for epidural morphine and interpretation was limited by publication bias detected in the included trials [8]. The broader question of dexamethasone's overall prophylactic anti-emetic efficacy remains unanswered.

In order to provide more robust and generalisable evidence, we therefore undertook this systematic review and meta-analysis to assess the prophylactic anti-emetic efficacy of i.v. dexamethasone in patients of either sex receiving any long-acting intrathecal or epidural opioids for any surgical procedure.

Methods

This investigation followed the recommended process described in the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement [9, 10]. We searched the following electronic databases up to April 2017: MEDLINE, Pubmed, Excerpta Medica database (Embase), the Cochrane Central Register of Controlled Clinical Trials (CENTRAL), Web of Science, and Latin American and Caribbean Center on Health Sciences Information (LILACS). No age or language limits were placed on the literature search, details of which are described in the Supporting Information. The search was, however, limited to randomised controlled trials and humans. Finally, the references of all articles retrieved from the search were manually scrutinised for any relevant trials not identified using the strategy described above, and Google Scholar™ was examined for any additional publications.

We aimed to include male or female patients undergoing any surgical operation under neuraxial anaesthesia only, who received long-acting neuraxial opioids. Only trials comparing i.v. dexamethasone with a control group were included in the present meta-analysis. We excluded trials investigating combinations of anti-emetics [11, 12], or administering dexamethasone neuraxially [13].

Extracted trial characteristics included: type of surgery; type of surgical anaesthesia (intrathecal or epidural); type, concentration and volume of neuraxial drugs administered; and dose of i.v. dexamethasone (Table 1). The quality of the research methodology of each randomised trial was assessed following the Cochrane Collaboration's risk of bias tool for randomised controlled trials [14]. Two authors (SG and IU) independently screened, reviewed and scored the items for each trial using this method and extracted data for the analyses. Disagreements over scoring or extracted data were resolved through discussion with a third author (EA). The specific outcomes sought from each article were derived following our standard approach, which we have described in three previous meta-analyses [15–17]. Initially, the planned primary outcome was the rate of postoperative nausea and vomiting at 24 postoperative hours, but this was changed after initial registration. After reading all included articles, the need for rescue anti-emetics during the first 24 postoperative hours was felt to represent a more robust surrogate of postoperative nausea and vomiting, and was more consistently reported. In addition, the reporting of this outcome permitted broader and more precise sub-group analyses, which allowed us to explore the hypotheses described below. Changes in the protocol are described in the section 'Revision notes' within the study registration. Secondary outcomes related to postoperative nausea and vomiting were the rates of: postoperative nausea; postoperative vomiting; or nausea and vomiting combined in the post-anaesthetic care unit and during the first 24 postoperative hours. Additional secondary outcomes were the rate of pruritus during the first 24 postoperative hours, and length of hospital stay. Secondary side-effect-related outcomes were rates of postoperative infection, restlessness and hyperglycaemia. The source study text, tables or graphs were used to extract means, SD, SEM, 95%CI, number of events and total number of participants. In situations where different doses were given, data from all groups were extracted. The authors of trials that failed to report the sample size or results as mean (SD) or 95%CI, were contacted up to three times by electronic mail to supply the missing or raw data. If no reply was obtained, the median, interquartile range (IQR) and range were used

Table 1 Trial characteristics.

Study	Group (n)	Dose of i.v. dexamethasone	Timing of study drug administration	Type of surgery	Surgical anaesthesia	Neuraxial local anaesthetic	Neuraxial opioid, dose, route of administration	Postoperative rescue anti-emetic drug	Primary outcome
Banihashem et al. [4]	Dexamethasone (25), Saline (27)	8 mg	Beginning of surgery	Caesarean section	Spinal	Lidocaine 75 mg	Meperidine 25 mg, intrathecally	Not specified	Unspecified
Cardoso et al. [27]	Dexamethasone (35), Saline (35)	10 mg	Beginning of surgery	Caesarean section	Spinal	Hyperbaric bupivacaine 15 mg	Morphine 60 μg, intrathecally	Not specified	Rate of PONV at 24 postoperative hours
Ho et al. [5]	Dexamethasone 2.5 mg (43), Dexamethasone 5 mg (42), Dexamethasone 10 mg (44), Saline (43)	2.5 mg, 5 mg, 10 mg	End of surgery	Total abdominal hysterectomy	Epidural	Lidocaine 2% with adrenaline 10 $\mu g.ml^{-1}$, 0.3 $ml.kg^{-1}$	Morphine 3 mg, epidurally	Intravenous ondansetron	Rate of PONV at 24 postoperative hours
Kadur et al. [28]	Dexamethasone (40), Saline (40)	0.1 $mg.kg^{-1}$, maximum 8 mg	Beginning of surgery	Lower limb orthopaedic surgery	Spinal	Hyperbaric bupivacaine 15 mg	Meperidine 15 mg, intrathecally	Intravenous ondansetron	Pain scores at 6 postoperative hours
Movafegh et al. [29]	Dexamethasone (29), Saline (28)	0.1 $mg.kg^{-1}$ maximum 8 mg	Beginning of surgery	Inguinal herniorraphy	Spinal	Hyperbaric bupivacaine 15 mg	Meperidine 15 mg, intrathecally	Not specified	Pain scores at 24 postoperative hours
Nortcliffe et al. [6]	Dexamethasone (30), Saline (30)	8 mg	End of surgery	Caesarean section	Combined spinal epidural	Hyperbaric bupivacaine 10 mg, intrathecally; intra-operative lidocaine 60–100 mg epidurally as needed	Fentanyl 10 μg and morphine 0.2 mg, both intrathecally	Intramuscular prochlorperazine	Rate of PONV at 24 postoperative hours
Tzeng et al. [7]	Dexamethasone (38), Saline (37)	8 mg	End of surgery	Caesarean section	Epidural	Lidocaine 2% with adrenaline 10 $\mu g.ml^{-1}$, 15–18 ml	Morphine 3 mg, epidurally	Intravenous metoclopramide	Need for rescue anti-emetics at 24 postoperative hours
Tzeng et al. [30]	Dexamethasone (38), Saline (38)	5 mg	End of surgery	Total abdominal hysterectomy	Epidural	Lidocaine 2% with adrenaline 10 $\mu g.ml^{-1}$, 0.3 $ml.kg^{-1}$	Morphine 3 mg, epidurally	Intravenous ondansetron	Rate of PONV at 24 postoperative hours
Wang et al. [31]	Dexamethasone (38), Saline (36)	8 mg	End of surgery	Total abdominal hysterectomy	Epidural	Lidocaine 2% with adrenaline 10 $\mu g.ml^{-1}$, 0.3 $ml.kg^{-1}$	Morphine 3 mg, epidurally	Intravenous metoclopramide	Rate of PONV at 24 postoperative hours
Wang et al. [32]	Dexamethasone 2.5 mg (44), Dexamethasone 5 mg (44), Dexamethasone 10 mg (43), Saline (44)	2.5 mg, 5 mg, 10 mg	End of surgery	Caesarean section	Epidural	Lidocaine 2% with adrenaline10 $\mu g.ml^{-1}$, 0.3 $ml.kg^{-1}$	Morphine 3 mg, epidurally	Intravenous ondansetron	Rate of PONV at 24 postoperative hours
Wang et al. [33]	Dexamethasone (39), Saline (37)	5 mg	End of surgery	Total abdominal hysterectomy	Epidural	Lidocaine 2% with adrenaline 10 $\mu g.ml^{-1}$, 0.3 $ml.kg^{-1}$	Morphine 3 mg, epidurally	Intravenous droperidol	Rate of PONV at 24 postoperative hours
Wu et al. [35]	Dexamethasone (42), Saline (42)	10 mg	End of surgery	Lower abdominal surgery	Epidural	Unspecified	Morphine 2 mg, epidurally	Not specified	Unspecified
Wu et al. [34]	Dexamethasone (30), Saline (30)	8 mg	Beginning of surgery	Caesarean section	Spinal	Hyperbaric bupivacaine 10 mg	Morphine 0.2 mg, intrathecally	Intravenous ondansetron	Rate of PONV at 24 postoperative hours

i.v., intravenous; PONV, postoperative nausea and vomiting.

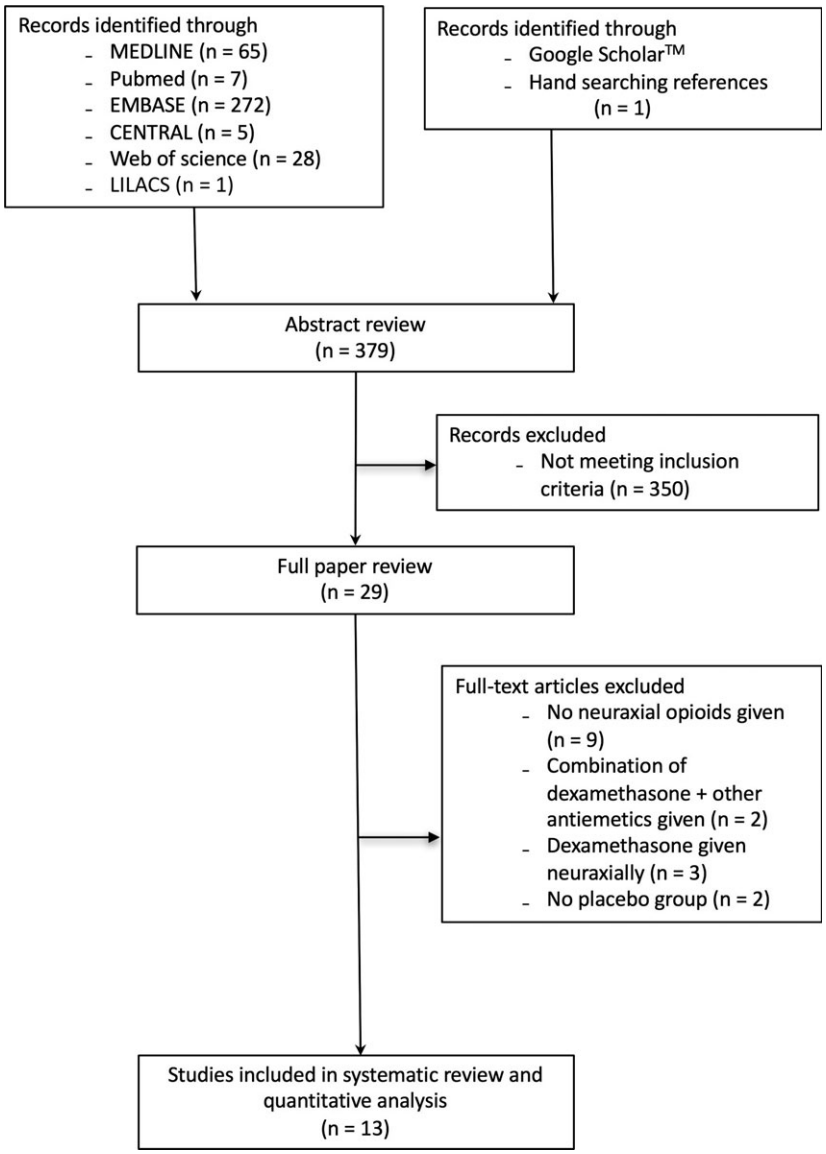


Figure 1 PRISMA flow diagram showing literature search results.

for mean (SD), as follows: the mean was estimated as equivalent to the median, and the SD was approximated by the IQR divided by 1.35, or the range divided by four [18]. Finally, we rated the quality of evidence for each outcome following the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system [19].

Meta-analyses were performed with the assistance of Review Manager software (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). This software estimates the weighted mean differences (MD) for continuous data and the risk ratio for categorical data between groups, with an overall estimate of the pooled effect. The coefficient I^2 was used to evaluate heterogeneity with predetermined thresholds for low (25–49%), moderate (50–74%) and high (> 75%) levels [20]. A random effects model was applied in case of moderate or high heterogeneity; otherwise a fixed effect model was used [21]. Our primary outcome, need for rescue anti-emetics during the first 24 postoperative hours, was analysed according to the dose of dexamethasone (low-dose 2.5–5.0 mg; intermediate dose 6.0–10.0 mg), timing of administration (beginning or end of surgery) and route of long-acting opioid injection (intrathecal or

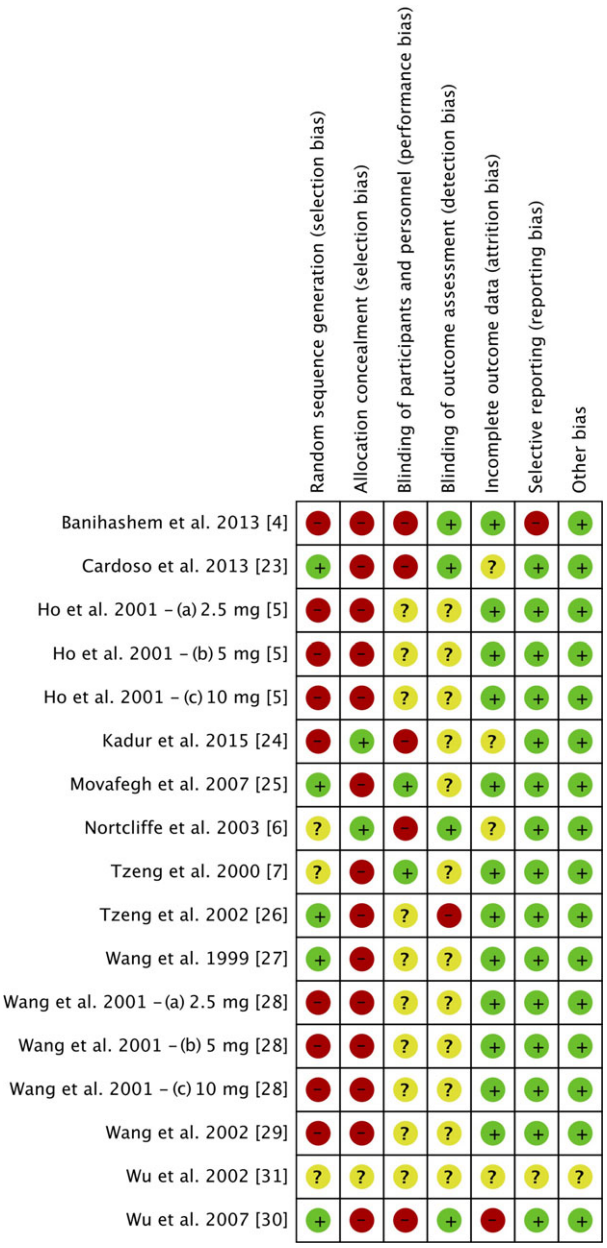


Figure 2 Evaluation bias risk for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias.

epidural) to account for heterogeneity. A sub-group analysis was performed to assess the impact of the total dose of i.v. dexamethasone on the need for rescue anti-emetics during the first 24 postoperative hours, using the JMP 9 statistical package (SAS Institute, Cary, NC, USA). The likelihood of publication bias was assessed by drawing a funnel plot [22] and confirmed with Duval and Tweedie's trim and fill test [23]. This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ, USA). Finally, a trial sequential analysis was executed on primary outcomes to confirm whether firm evidence was reached or not (TSA software version 0.9.5.5 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark) [24–26]. As the trial sequential analysis approach was initially designed for trials with low risk of bias and does not adjust for risk of bias, we repeated the analysis after excluding trials where most of the seven domains within the Cochrane Collaboration's Risk of Bias Tool were rated as being at 'high' or 'unclear' risk of bias. Results are presented as relative risk (RR) or MD (95%CI). A two-sided $p < 0.05$ was considered significant.

Results

From the literature search strategy, 379 citations were identified, 13 of which met the inclusion criteria, representing a total of 1111 patients (Fig. 1) [4–7, 27–35]. According to our assessment following the Cochrane Collaboration Risk of Bias Tool (Fig. 2), the majority of trials had a moderate to high risk of bias. Disagreements between authors either over bias scoring or extracted data occurred for four articles and were resolved after discussion with the third author [4, 27, 28, 32]. Attempts were made to contact three authors [6, 27, 34] but none provided the additional data requested.

Table 1 presents the trial characteristics of six trials which included patients scheduled for caesarean section [4, 6, 7, 27, 32, 34] and in four trials, patients were scheduled for total abdominal hysterectomy [5, 30, 31, 33]. The three remaining trials included patients who underwent lower limb surgery [28], inguinal herniorrhaphy [29] and lower abdominal surgery [35]. Five groups of authors administered i.v. dexamethasone at the beginning of surgery [4, 27–29, 34] and eight at the end [5–7, 30–33, 35]. Low (2.5–5 mg) and intermediate (6–10 mg) doses were injected in 4 [5, 30, 32, 33] and 11 trials [4–7, 27–29, 31, 32, 34, 35], respectively; two trials investigated several doses of dexamethasone [5, 32]. Three trials used intrathecal morphine [27, 34], three injected intrathecal meperidine [4, 29], and seven studied the epidural route [5, 7, 30–33, 35].

Intravenous dexamethasone significantly reduced the need for rescue anti-emetics during the first 24

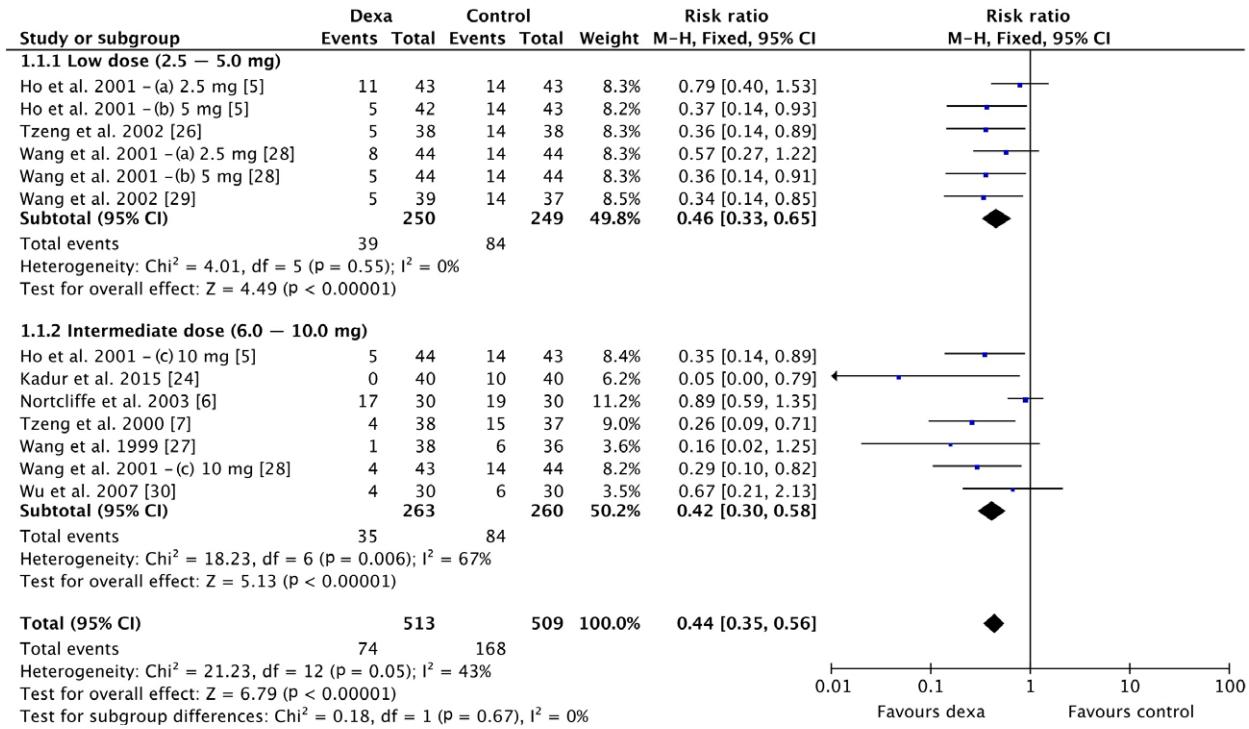


Figure 3 Forest plot of the effect of intravenous (i.v.) dexamethasone (dexa) on the need for rescue anti-emetics during the first 24 postoperative hours according to the dose (low-dose: 2.5–5.0 mg; intermediate dose: 6.0–10.0 mg).

postoperative hours, and there was no difference between low and intermediate doses (Fig. 3). The meta-regression showed no evidence of correlation between the i.v. doses administered or the risk ratio (r^2 = 0.07; p = 0.01; Fig. 4). A sub-group analysis by timing of administration showed that the risk ratios (95%CI) were 0.27 (0.10–0.74) and 0.46 (0.35–0.56) when dexamethasone was administered at the beginning or the end of surgery, respectively (p for sub-group difference = 0.32). Intravenous dexamethasone was effective regardless of the route of long-acting opioid administration, with the RR (95%CI) for intrathecal being and for epidural 0.61 (0.40–0.91); I^2 = 79%; p = 0.02} 0.40 (0.30–0.53); I^2 = 0%; p < 00001; p for sub-group difference = 0.10). The trial sequential analysis indicated that firm evidence was reached and that i.v. dexamethasone was superior to placebo (Fig. 5). This was further confirmed through a repeated analysis after removing trials at high risk of bias [5, 28, 32, 33]. With regard to the funnel plot for our primary outcome, the Duval and Tweedie's trim and fill test revealed the point estimates (95%CI) for the combined studies to be 0.34 (0.25–0.48), suggesting that no studies are missing. The quality of evidence for our primary outcome was moderate according to the GRADE working system.

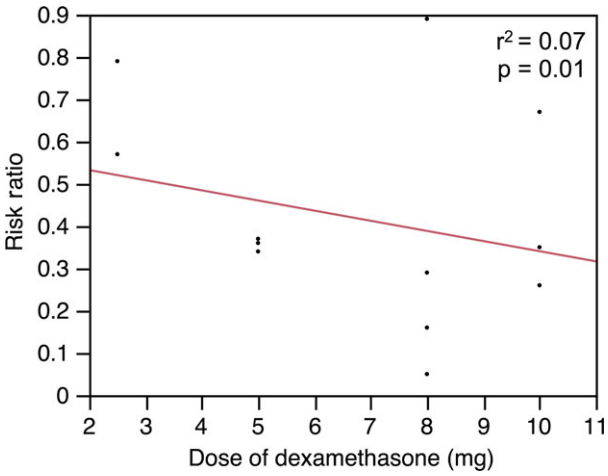


Figure 4 Meta-regression of intravenous (i.v.) dexamethasone dose and risk ratio of need for rescue anti-emetics during the first 24 postoperative hours.

Table 2 summarises the primary and secondary outcomes, together with the GRADE quality of

evidence assessments. All data are based on a fixed effect model, except for hospital length of stay. With respect to the GRADE assessments, we rated down by two levels for limitations and rated up for a large effect size, where present. Intravenous dexamethasone significantly reduced the rates of postoperative nausea, postoperative vomiting, and postoperative nausea and vomiting combined, at 24 h postoperatively (see Supporting Information, Table S1), without affecting the length of hospital stay (three trials [5, 30, 32]: MD (95%CI) −0.14 (−0.66 to 0.37); I^2 = 90; p = 0.59). Based on eight trials [4, 6, 7, 28, 29, 31, 33, 34], i.v. dexamethasone did not reduce the rate of pruritus at 24 postoperative hours, with a risk ratio (95%CI) of 0.89 (0.76–1.05), I^2 = 0%, p = 0.17. Among trials that recorded postoperative infections [4, 5, 7, 30, 32, 34] or restlessness at 24 postoperative hours [4, 7, 28, 30, 32, 34], no patients developed these complications and therefore no statistical analysis could be performed. Finally, none of the trials measured blood glucose levels.

Discussion

This systematic review and meta-analysis investigated the prophylactic anti-emetic efficacy of i.v. dexamethasone in patients of both sexes receiving any long-acting neuraxial opioids for any surgical procedure. Based on 13 randomised controlled trials, including a total of 1111 patients, our results show that i.v. dexamethasone reduces the need for rescue anti-emetics during the first 24 postoperative hours, along with the rates of postoperative nausea, postoperative vomiting, and postoperative nausea and vomiting combined, at 24 postoperative hours. Dexamethasone has anti-emetic

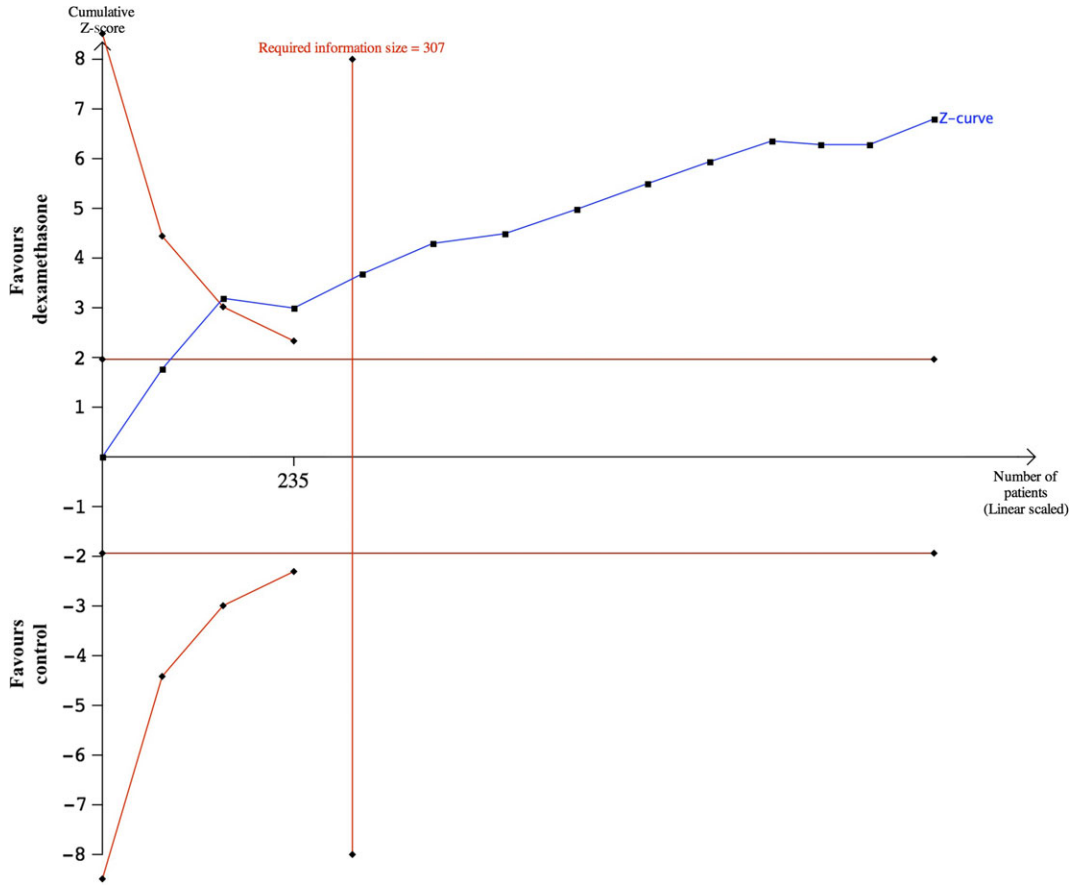


Figure 5 Trial sequential analysis on the need for rescue anti-emetics during the first 24 postoperative hours. The cumulative Z-curve (blue) crosses the monitoring boundary curve (red) and reaches the required information size, indicating firm evidence that intravenous dexamethasone is superior to placebo for this outcomes.

Table 2 Summary of findings. Values are number of events/number of patients

Outcome	Limitations	Dexamethasone	Control	RR (95%CI) or MD (95%CI)	p value for overall effect	Quality of evidence (GRADE)
Need for rescue anti-emetics during the first 24 postoperative hours	Blinding of participants, personnel and outcome assessor unclear in most studies	74/513	168/509	0.44 (0.35–0.56)	< 0.00001	Moderate quality due to limitations
Rate of postoperative nausea in post-anaesthetic care unit	Blinding of participants, personnel and outcome assessor unclear in most studies	11/35	26/35	0.42 (0.25–0.72)	0.001	Low quality due to limitations and imprecision
Rate of postoperative vomiting in post-anaesthetic care unit	Blinding of participants, personnel and outcome assessor unclear in most studies	11/35	23/35	0.48 (0.28–0.82)	0.008	Low quality due to limitations and imprecision
Rate of PONV in post-anaesthetic care unit	Blinding of participants, personnel and outcome assessor unclear in most studies	13/30	15/30	0.87 (0.50–1.49)	0.61	Very low quality due to limitations and imprecision
Rate of nausea at 24 postoperative hours	Blinding of participants, personnel and outcome assessor unclear in most studies	100/614	222/611	0.45 (0.37–0.55)	< 0.00001	Moderate quality due to limitations
Rate of vomiting at 24 postoperative hours	Blinding of participants, personnel and outcome assessor unclear in most studies	76/614	178/611	0.43 (0.34–0.54)	< 0.00001	Moderate quality due to limitations
Rate of PONV at 24 postoperative hours	Blinding of participants, personnel and outcome assessor unclear in most studies	102/455	242/451	0.42 (0.35–0.51)	< 0.00001	Moderate quality due to limitations
Rate of pruritus at 24 postoperative hours	Blinding of participants, personnel and outcome assessor unclear in most studies	110/269	122/265	0.89 (0.76–1.05)	0.17	Low quality due to limitations and imprecision
Hospital length of stay; days	Blinding of participants, personnel and outcome assessor unclear in most studies	298*	299*	−0.14 (−0.66 to 0.37)	0.59	Low quality due to limitations and imprecision

No trials reported rate of postoperative infection, rate of restlessness or blood glucose.
PONV, postoperative nausea and vomiting. *value is number of patients

properties regardless of whether it is administered at the beginning or at the end of surgery. It is effective in patients who receive long-acting opioids via the epidural as well as the intrathecal route. Despite the low likelihood of publication bias, we judged the GRADE evidence as moderate because of the unclear blinding of participants, personnel and outcome assessors in most studies.

The sub-group analysis showed that there was no difference between low doses and intermediate doses of dexamethasone; this was further confirmed by meta-regression. In dose-finding studies, two groups of authors have suggested that a ceiling effect is reached with a dose of 5 mg, whereas a dose of 2.5 mg is only partially effective [5, 32]. Nonetheless, as dexamethasone at a dose above 0.1 $mg.kg^{-1}$ confers an anti-inflammatory and an analgesic effect [36], administering an intermediate dose of 6–10 mg to patients receiving long-acting neuraxial opioids seems reasonable. This approach should be balanced against the knowledge that these doses may increase postoperative glucose levels by a mean of 1.3 $mmol.l^{-1}$ and 3.7 $mmol.l^{-1}$ in non-diabetic and diabetic patients, respectively [37].

Several limitations should be considered during interpretation of this meta-analysis. Although we attempted to explore the anti-emetic effect of dexamethasone in the post-anaesthetic care unit, only a limited number of trials sought outcomes related to postoperative nausea and vomiting during this time period. Also, although the coefficient of heterogeneity was low, many included trials suffered from unsatisfactory methodology, with high or unknown risk of selection bias (the absence of proper random sequence generation and allocation concealment) and performance bias (improper blinding of participants and personnel). Despite these concerns, our second trial sequential analysis performed after removing trials with high or unknown risk of bias confirmed the results of the initial analysis, indicating that no additional trials investigating this topic are required.

In conclusion, there is adequate evidence to state that i.v. dexamethasone provides effective anti-emetic prophylaxis during the first 24 postoperative hours in patients who receive long-acting neuraxial opioids, with a negligible risk of complications.

Acknowledgements

Our review protocol was registered on PROSPERO (CRD42017067407). We are grateful to Mrs I. von Kaenel (head librarian) and C. Jacques (librarian, Lausanne University Hospital, Lausanne, Switzerland) for their assistance with the literature search. This work was supported by departmental funding (Department of Anaesthesia, Lausanne University Hospital, Lausanne, Switzerland). EA has received grants from the Swiss Academy for Anaesthesia Research (SACAR), Lausanne, Switzerland and from B. Braun Medical AG, Sempach, Switzerland for other research projects. EA has also received an honorarium from B. Braun Medical AG. No other competing interests declared.

References

1. Pöpping DM, Elia N, Marret E, Wenk M, Tramèr MR. Opioids added to local anesthetics for single-shot intrathecal anesthesia in patients undergoing minor surgery: a meta-analysis of randomized trials. *Pain* 2012; **153**: 784–93.
2. Skolnik A, Gan TJ. Update on the management of postoperative nausea and vomiting. *Current Opinion in Anaesthesiology* 2014; **27**: 605–9.
3. Gan TJ, Diemunsch P, Habib AS, et al. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesthesia and Analgesia* 2014; **118**: 85–113.
4. Banihashem N, Hasannasab B, Alereza H. Does dexamethasone prevent subarachnoid meperidin-induced nausea, vomiting and pruritus after cesarean delivery. *Saudi Journal of Anaesthesia* 2013; **7**: 138–41.
5. Ho ST, Wang JJ, Tzeng JI, Liu HS, Ger LP, Liaw WJ. Dexamethasone for preventing nausea and vomiting associated with epidural morphine: a dose-ranging study. *Anesthesia and Analgesia* 2001; **92**: 745–8.
6. Nortcliffe SA, Shah J, Buggy DJ. Prevention of postoperative nausea and vomiting after spinal morphine for caesarean section: comparison of cyclizine, dexamethasone and placebo. *British Journal of Anaesthesia* 2003; **90**: 665–70.
7. Tzeng JI, Wang JJ, Ho ST, Tang CS, Liu YC, Lee SC. Dexamethasone for prophylaxis of nausea and vomiting after epidural morphine for post-Caesarean section analgesia: comparison of droperidol and saline. *British Journal of Anaesthesia* 2000; **85**: 865–8.
8. Allen TK, Jones CA, Habib AS. Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: a systematic review and meta-analysis. *Anesthesia and Analgesia* 2012; **114**: 813–22.
9. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *British Medical Journal* 2015; **349**: g7647.
10. Smith AF, Carlisle J. Reviews, systematic reviews and anaesthesia. *Anaesthesia* 2015; **70**: 644–50.
11. Imeh A, Olaniyi O, Simeon O, Omotola O. Dexamethasone versus a combination of dexamethasone and ondansetron as prophylactic antiemetic in patients receiving intrathecal

morphine for caesarean section. *African Health Sciences* 2014; **14**: 453–9.
12. Voigt M, Fröhlich CW, Hüttel C, et al. Prophylaxis of intra- and postoperative nausea and vomiting in patients during cesarean section in spinal anesthesia. *Medical Science Monitor* 2013; **19**: 993–1000.
13. Abdel-Aleem M, Osman A, Morsy K. Effect of coadministration of dexamethasone with intrathecal morphine on postoperative outcomes after cesarean delivery. *International Journal of Gynaecology and Obstetrics* 2012; **116**: 158–61.
14. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* 2011; **343**: d5928.
15. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. *Anaesthesia* 2015; **70**: 71–83.
16. Albrecht E, Mermoud J, Fournier N, Kern C, Kirkham KR. A systematic review of ultrasound-guided methods for brachial plexus blockade. *Anaesthesia* 2016; **71**: 213–27.
17. Grape S, Kirkham KR, Baeriswyl M, Albrecht E. The analgesic efficacy of sciatic nerve block in addition to femoral nerve block in patients undergoing total knee arthroplasty: a systematic review and meta-analysis. *Anaesthesia* 2016; **71**: 1198–209.
18. Choi SW, Lam DM. Trials and tribulations of a meta-analyst. *Anaesthesia* 2016; **71**: 228–31.
19. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**: 401–6.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002; **21**: 1539–58.
21. Choi SW, Lam DM. Heterogeneity in meta-analyses. Comparing apples and oranges. *Anaesthesia* 2017; **72**: 532–4.
22. Choi SW, Lam DM. Funnels for publication bias – have we lost the plot. *Anaesthesia* 2016; **71**: 338–41.
23. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000; **56**: 455–63.
24. Heesen M, Klimek M, Rossaint R, Imberger G, Straube S. Paravertebral block and persistent postoperative pain after breast surgery: meta-analysis and trial sequential analysis. *Anaesthesia* 2016; **71**: 1471–81.
25. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or rotational thromboelastometry (ROTEM) to monitor haemostatic treatment in bleeding patients: a systematic review with meta-analysis and trial sequential analysis. *Anaesthesia* 2017; **72**: 519–31.
26. Afshari A, Wetterslev J, Smith AF. Can systematic reviews with sparse data be trusted? *Anaesthesia* 2017; **72**: 12–6.
27. Cardoso MM, Leite AO, Santos EA, Gozzani JL, Mathias LA. Effect of dexamethasone on prevention of postoperative nausea, vomiting and pain after caesarean section: a randomised, placebo-controlled, double-blind trial. *European Journal of Anaesthesiology* 2013; **30**: 102–5.
28. Kadur SN, Ahmed F, Purohit A, Khandelwal M, Mistry T. The effect of intravenous dexamethasone on postoperative pain, nausea and vomiting after intrathecal pethidine and bupivacaine in lower limb orthopedic surgery. *Anaesthesia, Pain and Intensive Care* 2015; **19**: 254–9.
29. Movafegh A, Soroush AR, Navi A, Sadeghi M, Esfehani F, Akbarian-Tefaghi N. The effect of intravenous administration of dexamethasone on postoperative pain, nausea, and vomiting after intrathecal injection of meperidine. *Anesthesia and Analgesia* 2007; **104**: 987–9.
30. Tzeng JI, Hsing CH, Chu CC, Chen YH, Wang JJ. Low-dose dexamethasone reduces nausea and vomiting after epidural morphine: a comparison of metoclopramide with saline. *Journal of Clinical Anesthesia* 2002; **14**: 19–23.
31. Wang JJ, Ho ST, Liu YH, Ho CM, Liu K, Chia YY. Dexamethasone decreases epidural morphine-related nausea and vomiting. *Anesthesia and Analgesia* 1999; **89**: 117–20.
32. Wang JJ, Ho ST, Wong CS, Tzeng JI, Liu HS, Ger LP. Dexamethasone prophylaxis of nausea and vomiting after epidural morphine for post-Cesarean analgesia. *Canadian Journal of Anesthesia* 2001; **48**: 185–90.
33. Wang JJ, Tzeng JI, Ho ST, Chen JY, Chu CC, So EC. The prophylactic effect of tropisetron on epidural morphine-related nausea and vomiting: a comparison of dexamethasone with saline. *Anesthesia and Analgesia* 2002; **94**: 749–53.
34. Wu JI, Lo Y, Chia YY, et al. Prevention of postoperative nausea and vomiting after intrathecal morphine for cesarean section: a randomized comparison of dexamethasone, droperidol, and a combination. *International Journal of Obstetric Anesthesia* 2007; **16**: 122–7.
35. Wu YW, Xu JS, Chen ZQ, Gu MN, Wang YZ. Effects of dexamethasone on epidural morphine-related nausea and vomiting. *Di Yi Jun Yi Da Xue Xue Bao* 2002; **22**: 758–9.
36. De Oliveira GS, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2011; **115**: 575–88.
37. Tien M, Gan TJ, Dhakal I, et al. The effect of anti-emetic doses of dexamethasone on postoperative blood glucose levels in non-diabetic and diabetic patients: a prospective randomised controlled study. *Anaesthesia* 2016; **71**: 1037–43.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

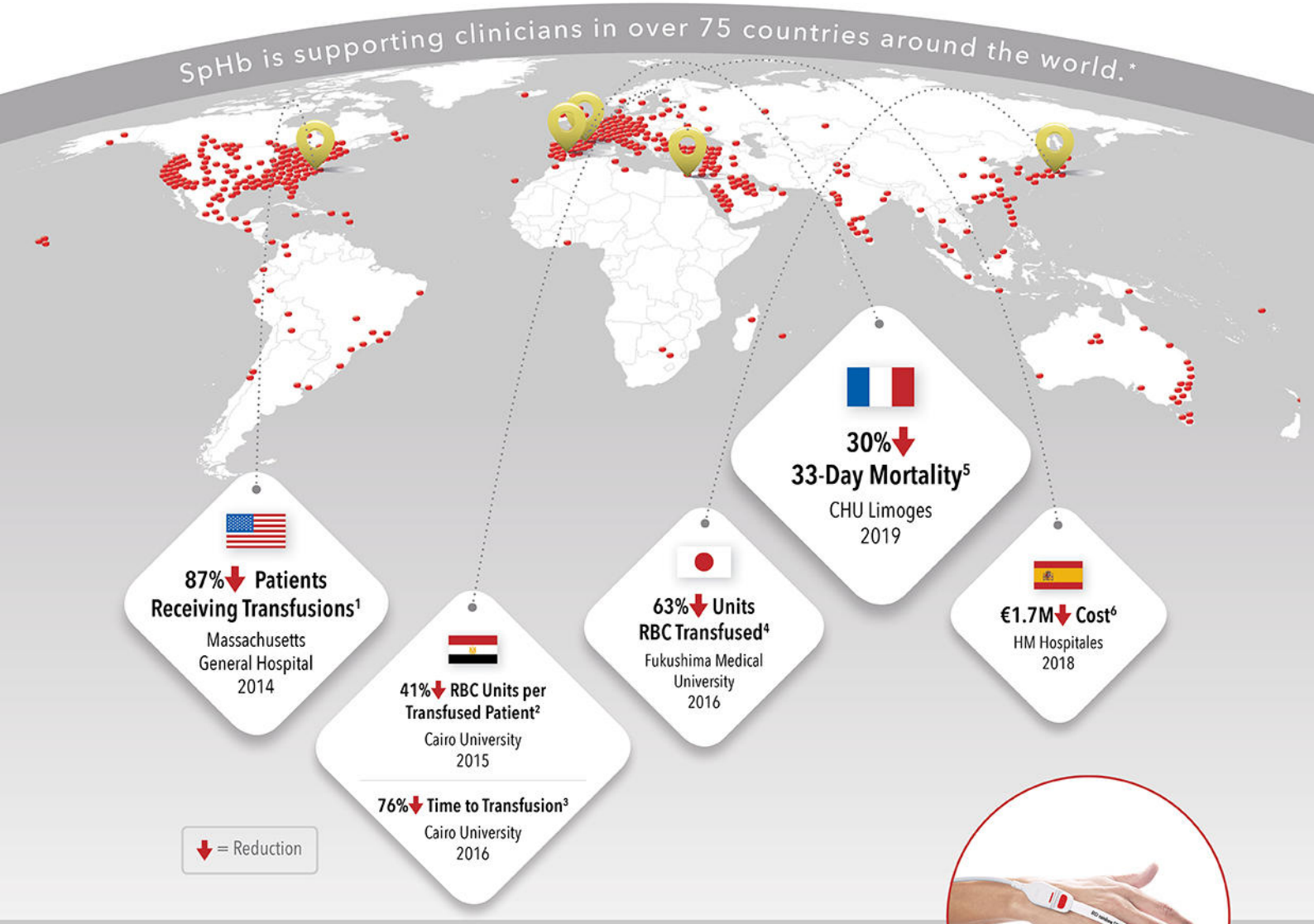
Table S1. Secondary PONV-related outcomes.

Patient monitoring partner
PHILIPS

Masimo

Are You Improving Outcomes with SpHb®?

Six studies across four continents have found that noninvasive and continuous haemoglobin (SpHb) monitoring can help improve outcomes[1-6]



Improve Your Outcomes with SpHb

Visit www.masimo.co.uk/sphb

For professional use. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering among other factors: patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. SpHb monitoring is not intended to replace laboratory blood testing. Blood samples should be analysed by laboratory instruments prior to clinical decision making.

[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9. [2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4. Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN·S Hematology Analyzer. [3] Kamal A, et al. *Open J of Anesth.* 2016 Mar; 6, 13-19. [4] Imaizumi et al. *Proceedings from the 16th World Congress of Anaesthesiologists* Hong Kong. Abstract #PR607. [5] Cros et al. *J Clin Monit Comput.* Aug 2019: 1-9. Study utilised a goal-directed fluid therapy protocol with PVi® in conjunction with a blood transfusion protocol based on SpHb. [6] Ribed-Sánchez B, et al. *Sensors* (Basel). 2018 Apr 27;18(5). pii: E1367. Estimated national savings derived from hospital savings extrapolated nationwide. * Data on file.

PLCO-003239/PLMM-11257A-1019
PLLT-10899B